Comprehensive genomic profiling of mucinous ovarian carcinoma with comparisons to mucinous colorectal carcinoma

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Abstract

Background

Advanced mucinous ovarian cancer (mOC) is a chemo resistant disease with poor outcomes compared to serous ovarian cancer (sOC). It is often confused with mucinous colorectal carcinoma (mCRC) metastatic to the ovary. Studies have explored CRC chemo regimens for the treatment of mOCs due to their histologic similarities. Herein we use comprehensive technologies to further our understanding of mOC

Methods

140 mOC specimens were evaluated by Caris Life Sciences from 2015 - 2018 using next generation sequencing (NGS), fragment analysis (FA), in situ hybridization (ISH), and immunohistochemistry (IHC). 188 mCRC were used for comparison. Chi square analysis was conducted using SPSS.

Results

The most frequent mutations in mOC were *KRAS* (64.7%), *TP53* (56.0%), *ARID1A* (50.0%), *CDKN2A* (18.7%), *PIK3CA* (11.7%), and *ATM* (8.2%). *ERBB2* (HER2) amplification was 12.2%. *BRCA1* and *BRCA2* mutation rates were 0.0 and 2.4%. Markers of immunogenicity were rare: MSI-H in 4.2%, high tumor mutational burden (TMB) in 4.8%, and PD-L1 expression in 5.3%.

Significant differences between mOC and CRC were found in the following pathways: Wnt (*APC*: 4.7 vs 61.7%), P13K/AKT/mTOR (*ARID1A:* 50.0 vs 0.0% and *FBXW7*: 3.7 vs 12.5%), MAPK (*BRAF*: 2.4 vs 11.9%), cell cycle control (*CDKN2A*: 18.7 vs 0.0%), as well as in *ERBB2* (HER2) amplification (12.2 vs 0.0%), and hormone receptor expression (ER: 12.8 vs 0.0%, PR: 15.9 vs 0.0%). High rates of KRAS (64.7, 73.5%) and TP53 (56.0, 46.7%) mutations were common to both tumor types.

Compared to mOC, right-sided CRC were more likely to have mutations in *CDH1* (0.0 vs 6.7%) and *PTCH1* (0.0 vs 6.7%), while left-sided CRC were more likely to have mutations in *FOXO3* (0.0 vs 5.9%) and *IDH2* (0.0 vs 5.9%).

Results

Age of mOC cohort	
Mean	51.9
Median	53.5
Range	18-84
Age of mCRC cohort	
Mean	61.2
Median	62
Range	25-89
Sex distribution in mCRC cohort	
Male	48.9% (92/188)
Female	51.1% (96/188)
mCRC specimen site profiled	
Colon	53.2% (100/188)

Figure 1. Patient Characteristics

Results

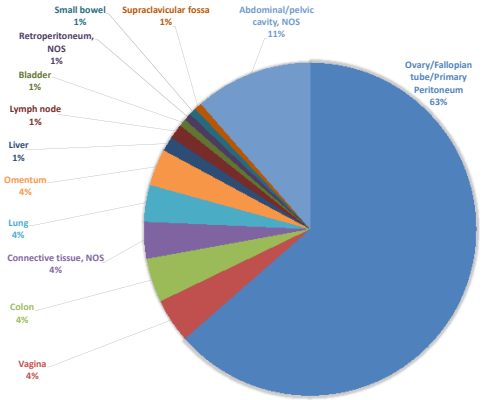

Figure 2. Tumor sites of mOC samples. Of the 140 mOCs evaluated, 63% were from the primary tumor on the ovary, falllopian tube, or peritoneum, 11% were from other locations in the abdomen and pelvis, 4% from the vagina, and 4% from the colon.

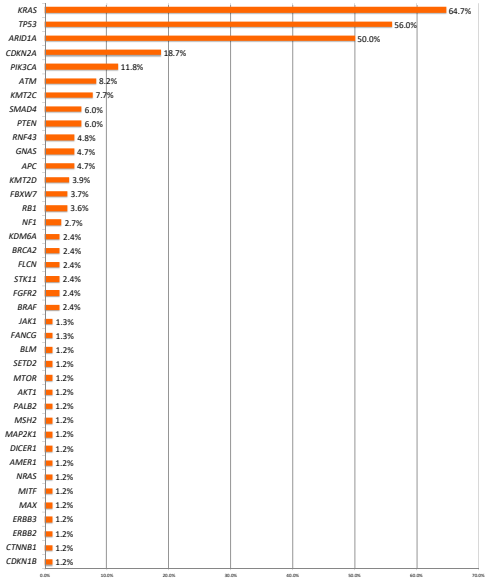

Figure 3. Next generation sequencing of mOC by whole exon sequencing using a 592 gene panel.

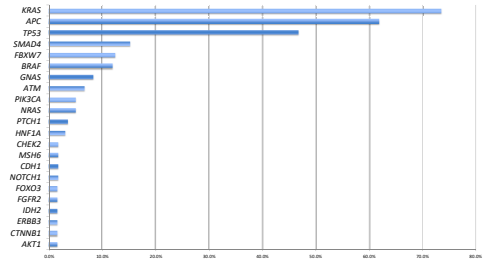

Figure 4. Next generation sequencing of mCRC by whole exon sequencing using a 592 gene panel.

Results

Pathway	Marker	Method	mOC %	mCRC %	
Wnt	*APC*	NGS	4.7	61.7	*
	CTNNB1	NGS	1.2	1.7	
PIK3CA/Akt/mTOR	*AKT1*	NGS	1.2	1.7	
	ARID1A	NGS	50.0	0.0	*
	FBXW7	NGS	3.7	12.5	*
	PIK3CA	NGS	11.8	5.1	
	PTEN (loss)	IHC	22.0	41.4	*
	PTEN	NGS	6.0	0.0	
	STK11	NGS	2.4	0.0	
MAPK	*BRAF*	NGS	2.4	11.9	*
	EGFR	NGS	0.0	0.0	
	ERBB2/HER2	CISH	12.2	0.0	*
	ERBB2/HER2	IHC	7.7	0.0	*
	ERBB2/HER2	NGS	1.2	0.0	
	ERBB4	NGS	0.0	0.0	
	KRAS	NGS	64.7	73.3	
	NRAS	NGS	1.2	5.0	
Cell cycle	*CDKN2A*	NGS	18.7	0	*
	RB1	NGS	3.6	0.0	
	TP53	NGS	0.0	0.0	
Hormone receptor	AR	IHC	6.3	2.0	
	ER	IHC	12.8	0.0	*
	PR	IHC	15.9	0.0	*
Immune modulatory	PD-L1	IHC	5.3	1.7	
	MSI	NGS	4.2	6.8	
	TMB	NGS	4.8	8.3	
HGF/cMET	MET	IHC	32	31.3	
MMR Pathway	MLH1 (loss)	IHC	2.9	8.5	
	MSH2 (loss)	IHC	1.5	1.7	
	MSH6 (loss)	IHC	2.9	2.9	
	PMS2 (loss)	IHC	2.9	9.1	
HRD Pathway	BRCA1	NGS	0	0	
	BRCA2	NGS	2.4	0	

* $p < 0.05$

Figure 5. Percentage of molecular and genomic aberration of mOCs and mCRCs organized by pathway.

Conclusions

- Our findings suggest that mOC is genomically distinct from mCRC and has multiple potential targets.
- At the molecular level, mOC may be differentiated from mCRC in cases of uncertain primary tumor
- A phenotype analysis with the presence of *ARID1A*, *CDKN2A*, HER2, ER or PR distinguishes mOC from mCRC, as does the absence of *CDH1*, *FOX03*, or *IDH2*.
- Dysregulation of the P13K/AKT/mTOR, cell cycle control, MAPK, and hormonal pathways may represent actionable targets in mOC.
- Understanding the molecular profile of this relatively uncommon histology may help direct future therapeutic trials in mOC.

References

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Authorship

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